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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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JAN 31 2001
PATENT & TRADEMARK OFFICE

In re application of:			
Joseph R. Byrum *et al.*		Art Unit:	1632
Appln. No.:	09/206,040	Examiner:	Scott D. Priebe
Filed:	December 4, 1998	Atty. Docket:	04983.0151.US01/ 38-21(15446)B
For:	Nucleic Acid Molecules and Other Molecules Associated with Plants		

APPELLANT'S BRIEF

Commissioner for Patents
Washington, DC 20231

Sir:

This is an Appeal from the Final Rejection of all claims pending in the above-described patent application. A Notice of Appeal was filed on September 13, 2000. The statutory fee of $310.00 for submitting this Brief is included in our attached Check No. 345393. *This Brief is submitted in triplicate.*

1. Real Party in Interest

The real party in interest is Monsanto Company, a Delaware corporation with offices at 800 North Lindbergh Boulevard, St. Louis, Missouri 63167. Monsanto Company is a subsidiary of Pharmacia Corporation, located at 100 Route 206 North, Peapack, New Jersey 07977.

2. Related Appeals and Interferences

The Appellant is unaware of any Appeals or Interferences related to this Appeal.

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3. Status of Claims

Claims 1-3 are pending. Claim 4 has been cancelled without prejudice. Claims 1-3 are independent. Claims 1-3 stand finally rejected under 35 U.S.C. §§ 101 and 112, first paragraph. Appellant appeals all of the rejections of each of the claims.

4. Status of Amendments

Applicants filed two Responses subsequent to Final Rejection in this case: a Response dated August 22, 2000 ("Applicants' Second Response") and accompanied by the Declaration of Roger C. Wiegand ("Wiegand Decl."), and a Response dated September 13, 2000 ("Applicants' Third Response") and accompanied by the Declaration of Thomas J. La Rosa ("La Rosa Decl."). All of these Responses and Declarations have been entered, per the Advisory Action (Paper No. 19) mailed on November 22, 2000 ("Advisory Action").

5. Summary of Invention

The invention is directed to nucleic acid molecules reciting the sequence of an expressed sequence tag ("EST") and its complement. The claimed nucleic acid molecules were derived from a cDNA collection prepared from young soybean pods (5 to 15 days after flowering). Specification at page 24, lines 4-5 and page 67, lines 11-12. More particularly, the present invention is directed to: a nucleic acid molecule isolated from other nucleic acid molecules and comprising SEQ ID No. 1 or its complement (claim 1); a nucleic acid molecule consisting of SEQ ID No. 1 or its complement (claim 2); and a nucleic acid molecule isolated from other nucleic acid molecules and consisting essentially of SEQ ID No. 1 or its complement (claim 3).

6. Issues

The issues in this Appeal are:

(a) whether claims 1-3 are unpatentable under 35 U.S.C. § 101 for allegedly being unsupported by a specific asserted utility or a well established utility;

(b) whether claims 1-3 are unpatentable under 35 U.S.C. § 112, first paragraph for alleged lack of enablement because the claimed invention purportedly lacks utility;

(c) whether claims 1 and 3 are unpatentable under 35 U.S.C. § 112, first paragraph for alleged lack of enablement because undue experimentation would supposedly be required to use the claimed nucleic acid molecules; and

(d) whether claims 1 and 3 are unpatentable under 35 U.S.C. § 112, first paragraph for alleged insufficiency of written description.

7. Grouping of Claims

Claims 1-3 remain in this case. Each claim is independent, and they do not stand or fall together. The separate patentability of these claims is addressed in Section 8 below. A copy of the claims on appeal is attached hereto as Appendix A.

8. Argument

A. Summary of Appellant's Position

As the Supreme Court said in *Brenner v. Manson*, the "basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility....where specific benefit exists in currently available form." 383 U.S. 519, 534-35, 148 U.S.P.Q. 689, 695 (1966). Applicants have met their part of the bargain – they have proven that the claimed nucleic acid molecules, in their current form, provide at least one specific benefit to the public, *e.g.*, the ability to identify the presence or absence of a polymorphism in a population of soybean plants.[1] This benefit is specific, not vague or unknown, and it is a "real world" or substantial benefit. Because the claimed nucleic acids provide at least this benefit, they satisfy the utility requirement of 35 U.S.C. § 101.

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[1] The Examiner has conceded that Applicants have proven this utility. Advisory Action at page 13.

Applicants have shown that the claimed nucleic acid molecules actually work for that and other utilities disclosed and described in the specification, and so both enablement rejections must be reversed. Applicants have proven that one skilled in the art is able to use the claimed nucleic acid molecules for at least two disclosed utilities, namely use to identify the presence or absence of a polymorphism and use as a hybridization probe for expression profiling. The law clearly establishes that the enablement requirement is satisfied if at least one mode of making and using the invention is enabled. Because Applicants have proven that the claimed nucleic acid molecules work for the disclosed utilities, the enablement requirement of 35 U.S.C. § 112 has been met.

Furthermore, Applicants have provided an adequate description of the claimed nucleic acids that demonstrates Applicants' possession of the claimed invention. The genus of claimed nucleic acid molecules, *i.e.*, nucleic acid molecules "comprising," "consisting of," and "consisting essentially of" SEQ ID No. 1 have been described by the recitation of a "basic and novel" common structural feature – the nucleotide sequence of SEQ ID No. 1 – which distinguishes them from nucleic acid molecules not in the claimed genus. Because the specification demonstrates that Applicants had possession of (and have provided an adequate description of) the claimed genus of nucleic acid molecules, the specification satisfies the written description requirement of 35 U.S.C. § 112.

B. The Wiegand and La Rosa Declarations Are Evidence That Substantiates the Utilities Established in the Specification

The Examiner has erroneously characterized the evidence presented by Applicants in the form of a Declaration under 37 C.F.R. § 1.132, *i.e.*, the Wiegand Declaration, as establishing utilities for the claimed invention rather than as evidence substantiating the utilities already established in the specification as filed. Relying on *In re Kirk* as a basis for this characterization, the Advisory Action stated:

> The Wiegand declaration presents further characterization of the claimed nucleic acid molecules that was not included in the original specification. Since this new information was not disclosed in the original specification, it could not be included in any evaluation of utility for the claimed invention...

Advisory Action at page 2.

This analysis misstates the nature of the Wiegand Declaration, ignores disclosed utilities, and is legally wrong. A declaration or affidavit submitted by an applicant is evidence that must be considered by the Patent Office when evaluating the patentability of an invention. *In re Alton*, 76 F.3d 1168, 1176, 37 U.S.P.Q.2d 1578, 1583-84 (Fed. Cir. 1996). *Accord In re Brana*, 51 F.3d 1560, 1567, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992); Revised Utility Examination Guidelines, 64 Fed. Reg. 71440, 71442 (Dec. 21, 1999); MPEP § 2107.02 at page 2100-33.

Moreover, the reliance on *In re Kirk* is misplaced. *Kirk* does not suggest that a declaration presenting evidence regarding utility is not evidence or should not be considered. In fact, the affidavit submitted in *Kirk* was considered, and found not to be dispositive on the utility issue, because it was directed to establishing that the claimed compounds had uses,[2] rather than to substantiating uses already disclosed in the specification.[3] *In re Kirk*, 376 F.2d 936, 941, 153 U.S.P.Q. 48, 53 (C.C.P.A. 1966).

Applicants agree with the Examiner that "the disclosure must have met the requirements of 35 U.S.C. 101 and 112, first paragraph at the time the application was filed." Advisory Action at page 2. Unlike *Kirk*, however, the present specification establishes utilities for the claimed nucleic acid molecules, *e.g.*, the identification and detection of polymorphisms. Specification at page 28, line 3 through page 35, line 3. Also unlike *Kirk*, the Wiegand Declaration provides

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[2] The affidavit proved that one skilled in the art would be able to determine the biological uses of the claimed compounds by routine tests, *i.e.*, the affidavit attempted to prove that "one skilled in the art would know how to use the claimed compounds." *In re Kirk*, 376 F.2d 936, 940-941, 153 U.S.P.Q. 48, 51-52 (C.C.P.A. 1966).

[3] The disclosed utility in *Kirk* was that the claimed compounds "have present and useful biological activity." 376 F.2d at 939, 153 U.S.P.Q. at 51.

experimental results substantiating the assertions in the specification that the claimed nucleic acid molecules may be successfully used for the utilities disclosed in the specification. *See, e.g.*, Wiegand Decl. at para. 23. A more analogous case to the present application is *In re Brana*, where the Federal Circuit held that:

> Enablement, or utility, is determined as of the application filing date. The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

In re Brana at 1567 n. 19 (citations omitted).

The Wiegand Declaration, like the declaration in *Brana*, submits experimental results showing that compounds within the scope of the claims exhibit the disclosed utilities. *E.g.*, Wiegand Decl. at paras. 19, 23. Also like the declaration in *Brana*, the Wiegand Declaration "goes to prove that the disclosure was in fact enabling [and useful] when filed." The law requires the Examiner to evaluate the Wiegand Declaration as evidence *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1583 (Fed. Cir. 1996).

C. The Claimed Nucleic Acids Have Legal Utility

Pending claims 1-3 were erroneously rejected under 35 U.S.C. § 101 because the claimed invention was allegedly not supported by either a "well-established utility" or a "specific asserted utility." Relying on *Brenner v. Manson* as a basis for asserting a lack of utility, the Final Action stated:

> the only apparent immediate utility for the EST, and therefore the claimed nucleic acid molecules, is further characterization of the EST, which includes characterization of undisclosed products made from or with the claimed nucleic acid molecules.

Final Action dated March 22, 2000 (Paper No. 14) ("Final Action") at page 16, *citing Brenner v. Manson*, 383 U.S. 519, 534-35, 148 U.S.P.Q. 689, 696 (1966). According to the Final Action,

"the application fails to disclose practical, real world utilities for the claimed nucleic acids comprising or consisting essentially of SEQ ID NO:1." Final Action at page 17.

This analysis misstates the nature of the asserted uses, ignores disclosed utilities, and misapplies the doctrine of "practical utility" developed by the courts after *Brenner v. Manson.* The "threshold for utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999), *citing Brenner v. Manson*, 383 U.S. 519, 534 (1966). Furthermore, an invention need only provide one identifiable benefit to satisfy 35 U.S.C. § 101. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983) ("when a properly claimed invention meets at least one stated objective, utility under section 101 is clearly shown").

The courts have expressed a test for utility that hinges on whether an invention provides an "identifiable benefit." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999), *citing Brenner v. Manson*, 383 U.S. 519, 534 (1966). For analytical purposes, the requirement for an "identifiable benefit" may be broken into two prongs: (1) the invention must have a specific, *i.e.*, not vague or unknown benefit, *In re Brana*, 51 F.3d 1560, 1565, 34 U.S.P.Q.2d 1436, 1440 (Fed. Cir. 1995); and (2) the invention must provide a real world, *i.e.*, practical or "substantial" benefit. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563, 39 U.S.P.Q.2d 1895, 1899 (Fed. Cir. 1996). A corollary to this test for utility is that the invention must not be "totally incapable of achieving a useful result," *i.e.*, the utility must not be incredible or unbelievable. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 U.S.P.Q.2d 1401, 1412 (Fed. Cir. 1992).

Applicants have not only asserted, but have substantiated their assertions with experimental proof that the claimed nucleic acid molecules provide identifiable benefits, *i.e.*, use to identify the presence or absence of a polymorphism, and use as a hybridization probe for

expression profiling. Either of these utilities alone is enough to satisfy Section 101. Because Applicants need only establish a single utility to satisfy 35 U.S.C. § 101, and they have done so in the present case, the premise of the rejection under Section 101 is incorrect, and the rejection should be reversed.[4]

(1) The Claimed Nucleic Acid Molecules Provide A Specific Benefit, *i.e.*, They Have Specific Utility

Applicants have asserted specific utilities for the claimed nucleic acid molecules in the specification, and have proven by experimentation that the claimed nucleic acid molecules work for at least two of the asserted utilities: use to identify the presence or absence of a polymorphism; and use as a hybridization probe for expression profiling. The law requires nothing more. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983) ("when a properly claimed invention meets at least one stated objective, utility under section 101 is clearly shown").

According to the Final Action, the disclosed utilities are not specific because they allegedly "lack the specific correspondence between the asserted utility and the claimed subject matter required by the statute." Final Action at page 8. It is unclear what the Final Action means by "specific correspondence." Apparently, the Final Action is asserting (inaccurately) that the disclosed utilities lack "specific correspondence" because the "only characteristic provided [for the invention] is a single nucleotide sequence" and characterization of, for example, the corresponding mRNA sequence and polypeptide sequence is "necessary for using the claimed EST in the disclosed utilities." Final Action at page 8; Advisory Action at page 3. In an attempt

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[4] Despite the Examiner's acknowledgement that the claimed invention is operable for at least one objective disclosed in the specification, *i.e.*, "the nucleic acid molecules do detect polymorphisms," Advisory Action at page 13, the utility rejection has been maintained. No legal basis has been provided in support of maintaining a utility rejection of an invention that meets the statutory criteria for utility. 35 U.S.C. § 131 states that "if on such examination [by the Patent Office] it appears that the applicant is entitled to a patent under the law, the Director shall issue a patent therefor." Applicants have proven that their claimed invention satisfies the statutory criteria of Section 101 as interpreted by the courts. This proof cannot be ignored.

to support these assertions, the Final Action calls them "facts." These purported "facts" are neither correct nor "facts."

First, it is not true that the only characteristic provided for the claimed nucleic acid molecules is a single nucleotide sequence. Applicants have disclosed a number of characteristics of the claimed nucleic acid molecules, including the identity of specific plant tissue expressing the corresponding mRNA, *i.e.*, young seed pods (5 to 15 days after flowering),[5] the origin of the clone from which SEQ ID No. 1 was sequenced, *i.e.*, *Glycine max* soybean cultivar Asgrow 3244, and the clone from which SEQ ID No. 1 was sequenced, *i.e.*, the clone designated "LIB3049-003-Q1-E1-H7." Specification at page 67, lines 11-12, page 24, line 4-5; Wiegand Decl. at para. 4; Sequence Listing at page 1. The Final Action ignored this disclosed information.

Second, Applicants have proven that the nucleotide sequence alone is all that is necessary to use the claimed nucleic acid molecules for the disclosed utilities, *e.g.*, to detect the presence or absence of polymorphisms. *See* Wiegand Decl. at paras. 22-23. The corresponding mRNA and polypeptide sequence need not be characterized. It is irrelevant whether the corresponding mRNA or polypeptide themselves have utility because Applicants are not relying on utility of the mRNA or polypeptide to establish utility of the claimed nucleic acid molecules.

In any event, it cannot be said that the disclosed utilities lack correspondence with the claimed invention, *i.e.*, nucleic acid molecules "comprising," "consisting of" and "consisting

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[5] The Advisory Action asserts that "young seed pods are not tissue, although they comprise tissues" and that the specification "does not disclose which specific tissue(s) contained in the young seed pods expressed the mRNA" and therefore that the claimed nucleic acid molecules have no utility. Advisory Action at pages 10-12. This distinction has no bearing on the utility of the claimed nucleic acid molecules. It was asserted that Applicants provided no characteristic for the claimed nucleic acid molecules other than "a single nucleotide sequence." Final Action at page 8. In response, Applicants pointed out the teachings in the specification of various characteristics of the claimed nucleic acid molecules, including the derivation of the claimed nucleic acid molecules from young seed pods. Applicants' Second Response at page 9. Whether or not young seed pods are "tissue" is irrelevant. One skilled in the art would know that because the claimed nucleic acid molecules were isolated from young seed pods, they will provide an appropriate starting point for isolating a promoter that is active in young seed pods. Utility of such a promoter is discussed in Section 8.C.(1)(c), *infra*.

essentially of" SEQ ID No. 1. One of the disclosed utilities for the claimed nucleic acids is the ability to identify the presence or absence of a polymorphism. Specification at page 28, line 3 through page 35, line 3. The Examiner has not provided any evidence suggesting that the claimed nucleic acid molecules, or indeed any nucleic acid molecule with an EST sequence, would not work for this utility. As the Wiegand Declaration demonstrates, the claimed nucleic acid molecule has been used to identify the presence of polymorphisms in a population of soybean plants. Wiegand Decl. at paras. 22-23. Because the claimed nucleic acid molecules work for the disclosed utilities, there is clearly a connection (correspondence) between the disclosed utilities and the claimed invention.

The specification also discloses additional utilities for the claimed nucleic acid molecules, including introduction of the claimed nucleic acid molecules into a plant or plant cell (either as sense or antisense inhibitors), which can then be used to screen for compounds such as a herbicide. Specification at page 64, line 19 through page 65, line 22.[6] For example, a compound can be provided to both an antisense plant and a control plant (no antisense) and the effect of the compound on the plant can be monitored. Such a screen is analogous to a cell-based assay, which has a legally sufficient utility.[7] Thus, the use in such a screen of a plant or plant cell having an introduced claimed nucleic acid molecule is a legally sufficient utility. Other utilities

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[6] The Examiner has questioned whether the disclosure is sufficient to practice antisense technology. Final Action at page 13; Advisory Action at page 18. However, no evidence has been provided supporting this position. Contrary to the assertions in the Advisory Action, the specification discloses use of the claimed nucleic acids as antisense molecules (*e.g.*, specification at page 64, lines 19-22), assays for detection of antisense activity (*see, e.g.*, the articles incorporated by reference at page 64, line 19 through page 65, line 22); and (3) utilities for antisense molecules (*e.g.*, specification at page 64, line 23 through page 65, line 7). Furthermore, Applicants are not required to teach "conventional and well-known genetic engineering techniques." *Ajinomoto Co. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345, 56 U.S.P.Q.2d 1332, 1337 (Fed. Cir. Oct. 3, 2000).

[7] *See, e.g.*, MPEP § 2107 at page 2100-25.

disclosed in the specification include use of the claimed nucleic acid molecules to measure the level of mRNA in a sample,[8] and use as molecular markers.[9]

(a) Use of the Claimed Nucleic Acid Molecules as Tools

The Final Action argued that these utilities are directed to use of the claimed nucleic acid molecules as tools, and that such utilities lack legal significance. Final Action at page 15; Advisory Action at pages 7, 9-10. This is wrong as a matter of law. The fact that, for example, a new and nonobvious microscope or screening assay can be used for learning about products or processes does not lessen the fact that such "tools" have legal utility. "Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have clear, specific and unquestionable utility (*e.g.*, they are useful in analyzing compounds)." MPEP § 2107 at page 2100-25.

One legal utility of a microscope is its use to look at the structure of biological tissues placed under the microscope (electron microscopes can, of course, be utilized to look at intracellular structures). Many of the disclosed utilities in this case are directly analogous to the utilities of a microscope, *i.e.*, the claimed nucleic acid molecules may be used to locate and

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[8] It is standard practice to screen populations of nucleic acids with EST sequences, often attached to a microarray, without characterizing each and every target mRNA. Knowing that the gene corresponding to the claimed nucleic acid molecules is expressed under certain conditions or in certain tissues or at certain levels is in itself useful. *See* Wiegand Decl. at para. 14. For example, such information is useful to detect expression changes in traits of interest, *e.g.*, drought stress. Contrary to the Advisory Action's assertions, this use is not using the claimed nucleic acid molecules as an "object of scientific inquiry." Advisory Action at page 12. It is a use of the claimed nucleic acid molecules, not a "scientific inquiry" performed on the claimed nucleic acid molecules.

[9] One can use the claimed nucleic acid molecules to determine location of a corresponding DNA sequence on a physical map or genetic map location without knowing anything beyond the claimed sequence. *See* Wiegand Decl. at para. 12. The use of molecular markers is a practical activity in the development of nutritionally enhanced or agriculturally enhanced crops. Such markers are useful in, for example, genetic mapping or linkage analysis, marker-assisted breeding, physical genome mapping, transgenic crop production, crop monitoring diagnostics, and gene identification and isolation. As more markers are identified, genetic maps will become more detailed and it will be easier for plant breeders to breed for particular traits. *See* Applicants' Second Response at pages 11-12 and articles referenced therein. The Advisory Action attacks the credibility of this utility by refusing to acknowledge Applicants' evidence as presented in the Wiegand Declaration. As is explained in Section 8.B, *supra*, declaratory evidence cannot be ignored.

measure nucleic acid molecules within a sample, cell, or organism. The Advisory Action denigrates this utility by asserting that the "only nucleic acid molecules that could be located or measured are nucleic acid molecules embraced by the claims." Advisory Action at page 9. The Advisory Action also asserts that the "claimed nucleic acid molecule can only be used [*e.g.*, in a screening assay] to identify a nucleic acid molecule complementary to itself." Advisory Action at page 10.

These assertions are not true. The claimed nucleic acid molecules may be used to locate and measure nucleic acid molecules such as mRNA or chromosomal DNA that hybridize to, but that do not consist of, consist essentially of, or comprise SEQ ID No. 1 or its complement. For example, an mRNA having 90 percent homology to SEQ ID No. 1 over a 100 base pair stretch could be located by the claimed nucleic acid molecules, as could a segment of chromosomal DNA having 85 percent homology over a 75 base pair stretch with the complement of SEQ ID No. 1. Neither the mRNA nor the chromosomal DNA segment are embraced by the claims of the present invention.

(b) Identifying the Presence or Absence of a Polymorphism

One of the utilities disclosed in the specification is use of the claimed nucleic acid molecules to identify the presence or absence of a polymorphism. Specification at page 28, line 3 through page 35, line 3. Two arguments have been presented in an attempt to attack the utility of this use. First, the Final Action suggests that without the prior identification of a polymorphism, such use is legally insufficient "use testing." Final Action at pages 9-10. Second, the Advisory Action suggests that identification of the presence or absence of a polymorphism, like a biological assay, has no utility "[i]f such an assay would only identify compounds that have no utility." Advisory Action at page 12. Both of these suggestions are wrong.

First, the Final Action provides no support (legal or factual) for the proposition that before detection of polymorphisms can be recognized as a legal utility, actual polymorphisms must be shown to exist. This proposition suggests that a gas chromatograph is not useful for detection of chemical compounds until actual chemical compounds are proven to exist. Moreover, use of the claimed nucleic acid molecules to screen for polymorphisms is not "use testing" because it determines information about the plant and its genetic traits, not additional information about the claimed nucleic acid sequence.

The Advisory Action confuses use of the claimed nucleic acid molecules with "use testing." The Final Action challenged the credibility of the use to identify the presence or absence of a polymorphism. Final Action at page 10. Applicants, while maintaining that the Examiner's challenge did not raise a proper *prima facie* case of non-utility, presented experimental evidence demonstrating that the claimed nucleic acid molecules are operable, *i.e.*, that they work successfully to identify the presence or absence of a polymorphism. Wiegand Decl. at paras. 22-23; Applicants' Second Response at pages 10-11. The Advisory Action now attempts to wave *In re Kirk* like a magic wand and convert this proof of operability into "use testing."[10] Advisory Action at pages 12-13. This cannot be done. The facts of *Kirk* are not similar to the present application,[11] and *Kirk*'s condemnation of applications that fail to disclose any use for a claimed invention is clearly not applicable to the present application, which discloses multiple uses for the claimed nucleic acid molecules. *E.g.*, specification at page 28,

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[10] The Advisory Action also asserts that the experiments performed by Dr. Wiegand were "necessary before one could begin to take the next step in determining how to exploit this characteristic of the claimed invention for a practical utility." Advisory Action at page 13. This is not true. The experiments themselves demonstrate a practical utility for the claimed nucleic acid molecules. The Advisory Action misses the "simple, incontrovertible fact" that the use of the claimed nucleic acid molecules to identify the presence or absence of polymorphisms is a use of the claimed nucleic acid molecules, not a preparatory step for another use.

[11] For an explanation of *Kirk* and an illustration of how it differs from the present specification, *see* Section 8.B, *supra*.

line 3 through page 35, line 3 (identify the presence or absence of polymorphisms), page 38, line 23 through page 41, line 18 (detect the expression level/pattern of a protein or mRNA), etc.

Use of the claimed nucleic acid molecules to detect the presence or absence of polymorphisms is no more legally insufficient than using a gas chromatograph to analyze the chemical composition of a gas – such use determines information about the gas, not the gas chromatograph. Even if the gas chromatograph detects the absence of a particular chemical element in the gas, that finding does not obviate the utility of the gas chromatograph itself. Information has been obtained about the gas.[12] Likewise, the claimed nucleic acid molecules have utility even if the absence of a particular polymorphism is detected. Indeed, the absence of a polymorphism usefully demonstrates that the two (or more) populations being compared share a common genetic heritage.

The Advisory Action argues that a screening assay, such as a cell-based screening assay "would only meet the utility requirement if certain conditions were met....[including that] the specification would have to teach some practical utility for at least one ligand identified by the assay, e.g. use as a drug." Advisory Action at page 10. This argument implies that a diagnostic test such as an ELISA has no patentable utility because it does not identify useful ligands. This result is absurd. Furthermore, contrary to the Advisory Action's assertions, *Brenner v. Manson* does not hold that a screening assay does not meet the utility requirement. *Brenner* holds that a process which has no known use (or a process which has the sole known use of producing a compound which has no known use) is not patentable. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 U.S.P.Q. 689, 693-94 (1966). The utility of a screening assay such as a diagnostic assay

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[12] For example, gas sampled from crude oil may be analyzed by gas chromatography for the presence or absence of chlorine, which is toxic to catalysts used in gasoline refining even in very low concentrations. The absence of a peak at the molecular weight of chlorine indicates the absence of chlorine in the sample being tested, thereby providing useful information (no chlorine is present, therefore the catalyst will not be destroyed) to the refinery manager. *See, e.g.*, U.S. Patent No. 6,133,740 entitled "Chlorine Specific Gas Chromatographic Detector."

is known, *i.e.*, use as a diagnostic tool.[13] Therefore, it is not prohibited from patentability by *Brenner*. Likewise, the utility of identifying the presence or absence of a polymorphism is known, *i.e.*, it demonstrates whether two (or more) organisms being compared do or do not share a common genetic heritage.

In any event, these arguments are beside the point because the claimed nucleic acid molecules did identify a polymorphism. The Declaration of Dr. Wiegand reports that a nucleic acid molecule having the sequence of SEQ ID No. 1 detects polymorphisms in soybean chromosomal DNA from the soy varieties *Glycine max* and *Glycine soja*. Wiegand Decl. at paras. 22-23. The Declaration also confirms that nucleic acid molecules capable of detecting polymorphisms are useful in plant breeding. *Id.* at paras. 20, 23. The Advisory Action asserts, without support, that the Wiegand Declaration does not substantiate the disclosed utility of detecting polymorphisms because the specification defines polymorphisms as intraspecies variations and *Glycine max* and *Glycine soja* are "two different species of *Glycine*." Advisory Action at page 13. This is not true. *Glycine max* and *Glycine soja* can be interbred to produce fertile offspring.[14] Therefore the Wiegand Declaration does substantiate the disclosed utility.

The claimed nucleic acid molecules have been proven to work for a specific, *i.e.*, not vague or unknown benefit – they identify the presence or absence of a polymorphism. This benefit is immediately realized directly from the use of the claimed nucleic acids, not from the use of other molecules. Such a proven use that provides an acknowledged known benefit to the public satisfies the utility requirement of 35 U.S.C. § 101.

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[13] In other words, the screening assay's utility arises from its ability to tell the practitioner if a blood or body fluid sample is infected with a disease organism, or not. *E.g.*, U.S. Patent Nos. 6,153,411 (issued November 28, 2000); 6,140,055 (issued October 31, 2000); and 6,120,776 (issued September 19, 2000).

[14] A species, by definition, is a group of organisms that are "able to interbreed and produce fertile offspring." Norah Rudin, DICTIONARY OF MODERN BIOLOGY 346 (1997); OXFORD DICTIONARY OF BIOCHEMISTRY AND MOLECULAR BIOLOGY 610 (A. D. Smith et al. eds., 1997).

(c) Probes for Other Molecules or Source for Primers

Other uses for the claimed nucleic acid molecules are as probes for other molecules or as a source of primers. The Final Action suggests that these uses are not legal utilities because the specification has not disclosed any specific nucleic acid molecule that can be identified using the claimed nucleic acid molecules. Final Action at pages 12-13; Advisory Action at page 16. This is not correct. The specification discloses that the claimed nucleic acid molecules can be used to isolate nucleic acid molecules of other plants and organisms such as alfalfa, rice, potato, cotton, oat, rye, barley, maize, wheat, *Arabidopsis*, *Brassica*, *etc.*[15] Specification at page 24, lines 13-26. The Final Action has not provided any evidence that would reasonably suggest that this cannot be done.

One illustrative example of a molecule that can be isolated using the claimed nucleic acid molecules is the promoter of the gene corresponding to the claimed nucleic acid molecules. Applicants have specifically disclosed that one use of the claimed nucleic acid molecules is to initiate a chromosome walk. Specification at page 25, lines 26-27. The Final Action denigrates that utility when it asserts that the claimed nucleic acid molecules "at best...can be used to initiate a 'chromosome walk' cloning procedure" and that "[a]ny nucleic acid molecule from any plant cell generally serves this purpose...." Final Action at page 13. *See also* Advisory Action at pages 16-17.

In short, the Final Action appears to be arguing that the utility is not a legal utility simply because other molecules can be used for the same purpose, *i.e.*, chromosome walks. That position is wrong as a matter of law – there is no requirement of exclusive utility in the patent law. *See Carl Zeiss Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 U.S.P.Q.2d 1094, 1100 (Fed. Cir. 1991) ("An invention need not be the best or the only way to accomplish a certain

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[15] Furthermore, one skilled in the art of hybridization and amplification understands how to design and utilize probes and primers to target a sequence of interest, and therefore it is not necessary for Applicants to provide a laundry list of each and every nucleic acid molecule that can be identified using the claimed nucleic acid molecules.

result..."). Such an argument would imply that a new golf club has no legal utility because other golf clubs can be used for the same purpose, *i.e.*, hitting golf balls. That position must be rejected as it requires reading "into the patent laws limitations and conditions which the legislature has not expressed," a practice condemned by the Supreme Court. *See Diamond v. Chakrabarty*, 447 U.S. 303, 308, 206 U.S.P.Q. 193, 196 (1980), *quoting United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 199, 17 U.S.P.Q. 154, 162 (1933).

Moreover, it is factually incorrect that random nucleic acid molecules would provide as good a starting point for a chromosome walk as would the claimed nucleic acid molecules. The claimed nucleic acid molecules provide a particularly appropriate and demonstrably useful starting point for a walk to isolate a promoter that is active in young seed pods (5 to 15 days after flowering). It is also factually incorrect that there is no well-established use for such a promoter, as is asserted in the Advisory Action at pages 16-17. Isolation of such a promoter would be desirable and particularly useful because it allows expression of proteins at that important developmental state, including proteins that provide disease resistance. Because the claimed nucleic acid molecules were isolated from young seed pods, they provide an appropriate starting point for isolating a promoter active in young seed pods. A random nucleic acid molecule does not provide an equally good starting point to isolate such a promoter. Furthermore, even if a random nucleic acid molecule provided a <u>better</u> starting point than the claimed nucleic acid molecules, it would not obviate the utility of the claimed nucleic acid molecules. An invention may be "less effective than existing devices but nevertheless meet the statutory criteria for patentability." *Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 960 n.12, 1 U.S.P.Q.2d 1196, 1199 n.12 (Fed. Cir. 1986).

In further challenging the utility, the Final Action asserts that the "chromosome walk" might be quite long. But the question is not whether the claimed nucleic acid molecules would necessitate a long "walk," but whether the claimed nucleic molecules will <u>work</u> for the disclosed

use. The Final Action has failed to provide evidence, or even to suggest a reason for believing that the claimed nucleic acid molecules could not be so used. Accordingly, the assertion of this utility as a probe for other molecules or as a source of primers satisfies the requirements of 35 U.S.C. § 101. *See In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995).

Perhaps in recognition of the foregoing inadequacies in the rejection, the Final Action also asserts that Applicants provide no information that would allow those of ordinary skill in the art to recognize when a promoter is located. Final Action at page 13; Advisory Action at page 17. That assertion is incorrect. Applicants have specifically directed the art worker toward Birren *et al.*, *Genome Analysis: Analyzing DNA*, Cold Spring Harbor Laboratory Press, Plainview, NY (1997), which provides such information. Specification at page 26, lines 12-15. It is doubtful that even that direction was necessary, but certainly nothing more is required. *See Ajinomoto Co. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345, 56 U.S.P.Q.2d 1332, 1337 (Fed. Cir. Oct. 3, 2000) (no requirement to teach "conventional and well-known genetic engineering techniques").

(2) The Claimed Nucleic Acid Molecules Provide Practical, Real World Benefits, *i.e.*, They Have Substantial Utility

It appears that the Final Action is arguing that the disclosed uses are legally insufficient or "insubstantial" under 35 U.S.C. § 101,[16] but such an argument has no basis in law. The touchstone of "substantial" utility is "real world" or "practical utility." *See, e.g., Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563, 39 U.S.P.Q.2d 1895, 1899 (Fed. Cir. 1996). "'Practical utility' is a shorthand way of attributing 'real world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate

[16] The Advisory Action asserts that the "specification does not disclose any particular significance of the claimed nucleic acid molecules; and discloses no purpose, 'real-world' benefit in readily apparent form for the claimed molecules." Advisory Action at page 7. While the meaning of "particular significance" is unclear, the reference to a "real world" benefit obviously refers to the utility issue.

benefit to the public." *Nelson v. Bowler*, 626 F.2d 853, 856, 857, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980) ("tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use").[17]

There can be no question that one skilled in the art can use the claimed nucleic acid molecules in a manner which provides an immediate benefit to the public. *E.g.*, Wiegand Decl. at paras. 20, 23. Applicants have disclosed numerous utilities for the claimed nucleic acid molecules, and have submitted evidence proving that the claimed nucleic acid molecules work for at least two of the disclosed utilities. *See* Wiegand Decl. Furthermore, Applicants have proven that the claimed nucleotide sequence alone, *i.e.*, the claimed invention in "readily apparent form," is all that is necessary to use the claimed nucleic acid molecules for the disclosed utilities, *e.g.*, to detect the presence or absence of polymorphisms. *See* Wiegand Decl. at paras. 22-23. The detection of polymorphisms provides an immediate benefit to the public because, *e.g.*, it "enables a plant breeder to determine the distribution of parental genetic material in the progeny of a cross." Wiegand Decl. at para. 20. Because the evidence of pharmacological activity in *Nelson* was deemed to provide an immediate benefit and thus a practical utility, the tests submitted here which evidence detection of a polymorphism must likewise be deemed to evidence practical utility.

Quite apart from the detection of polymorphisms, there is also no question that the public has recognized the benefits provided by the claimed subject matter, and has attributed "real world" value to such nucleic acid molecules. As noted in Applicants' First Response, the utility of ESTs is not merely an academic issue; [18] the real world value of ESTs is self-evident from the

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[17] *Accord Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739, 747-48 (Fed. Cir. 1985); *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 1383, 181 U.S.P.Q. 453, 454 (C.C.P.A. 1974).

[18] The Advisory Action confuses the issue by attacking the utility of EST databases and libraries. *See* Advisory Action at pages 7-9. Applicants are not claiming EST databases and libraries. Applicants provided evidence proving the commercial value of EST databases and libraries, as well as the commercial value of nucleic acid molecules with EST sequences alone in response to the Examiner's concerns that the claimed invention lacked a "practical" or "real-world use." Final Action at page 17. The thrust of Applicants' position is not that the utility of

growth of a multi-million dollar industry in the United States premised on the usefulness of ESTs. *See* Wiegand Decl. at para. 6. Like fermentation processes involving bacteria, ESTs and nucleic acid molecules with EST sequences are "industrial product[s] used in an industrial process – a useful or technical art if there ever was one." *See, e.g., In re Bergy*, 563 F.2d 1031, 1038, 195 U.S.P.Q. 344, 350 (C.C.P.A. 1977).

The Final Action misapprehends the commercial value of ESTs. Nucleic acid molecules with EST sequences are bought and sold in the biotechnology industry, as are microarrays composed of nucleic acid molecules with EST sequences.[19] In addition, many biotechnology companies derive significant revenue from EST technology. Such technology is often licensed through agreements that require the transfer of either the clones from which the ESTs were obtained, or the information necessary to make nucleic acid molecules with the EST sequences. Wiegand Decl. at para. 6. The Final Action is clearly in error when failing to credit the value of the underlying sequenced clones, *i.e.*, the nucleic acid molecules. Indeed, it is wrongly asserted that the molecules themselves have no value in the multi-million dollar industry that has developed.[20]

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an EST arises from its commercial value, but that ESTs have utility that is commercially valuable. Applicants' evidence proving that nucleic acid molecules with EST sequences are bought and sold and have commercial value was not meant to be interpreted as suggesting that any item that is bought and sold has patentable utility. The evidence was submitted as proof that nucleic acid molecules with EST molecules, such as the claimed nucleic acid molecules, are "related to the world of commerce."

[19] *E.g.*, Gene Logic, Inc. builds its EST expression databases using Affymetrix's GeneChip® probe arrays, which it licenses from Affymetrix. GeneChip® probe arrays are composed of hundreds of nucleic acid molecules with EST sequences. *See* "Gene Logic To Use Affymetrix GeneChip Arrays to Build Gene Expression Database Product," Press Release, January 11, 1999 (http://www.genelogic.com/PR-GeneChip.htm), document AR3 in the Information Disclosure Statement filed July 6, 1999.

[20] The Advisory Action casts aspersions on Applicants' evidence, because it does not "explain why purchasers consider the databases (and associated clones) valuable." Advisory Action at page 8. This is an irrelevant argument. Applicants have proven the utility of the claimed invention in the Wiegand Declaration. They have also proven that purchasers consider nucleic acid molecules with EST sequences valuable, *i.e.*, purchasers are willing to pay money for these molecules. In sum, Applicants have proven that the claimed invention has utility and is commercially valuable. Therefore, the Final Action's assertion that the molecules themselves have no "real world" benefit is clearly false.

According to the Final Action, this commercial success is not proof of the real world value of ESTs because commercial success is impacted by a variety of factors such as advertising and marketing. Final Action at page 7. No evidence was cited in support of this assertion. The market participants for EST products are primarily sophisticated corporations and highly knowledgeable scientists who are unlikely to make commercial and scientific decisions regarding the value of ESTs based on how the ESTs are advertised. Just as "[p]eople rarely, if ever, appropriate useless inventions," they rarely, if ever, pay for useless inventions. *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 U.S.P.Q. 592, 599 (Fed. Cir. 1983).

Quite simply, the commercial value of ESTs is proof of their real world value and of the benefits they provide to the public. This evidence cannot be ignored. The patent system was created to serve and foster growth and development in the industrial arts. If the industries themselves recognize and appreciate the value of an invention, it is not for the Patent Office to say that they are mistaken.

(3) The Disclosed Utilities Are Credible to One of Skill in the Art

An assertion of utility must be accepted by the Examiner unless it would not be considered "credible" by a person of ordinary skill in the art. MPEP § 706.03(a)(1). Cases in which utility was found not to be credible are rare, and usually involve "hare-brained" utilities.[21] A challenge to the credibility of a utility is essentially a challenge directed to operability, and

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[21] Examples of incredible utilities are given in MPEP § 2107 at page 2100-26, and include:

> an invention asserted to change the taste of food using a magnetic field (*Fregeau v. Mossinghoff*, 776 F.2d 1034, 227 U.S.P.Q. 848 (Fed. Cir. 1985)), a perpetual motion machine (*Newman v. Quigg*, 877 F.2d 1575, 11 U.S.P.Q. 1340 (Fed. Cir. 1989)), a flying machine operating on "flapping or flutter function" (*In re Houghton*, 433 F.2d 820, 167 U.S.P.Q. 687 (C.C.P.A. 1970)), a method for increasing the energy output of fossil fuels upon combustion through exposure to a magnetic field (*In re Ruskin*, 354 F.2d 395, 148 U.S.P.Q. 221 (C.C.P.A. 1966)), uncharacterized compositions for curing a wide array of cancers (*In re Citron*, 325 F.2d 248, 139 U.S.P.Q. 516 (C.C.P.A. 1963)), a method of controlling the aging process (*In re Eltgroth*, 419 F.2d 918, 164 U.S.P.Q. 221 (C.C.P.A. 1970)), and a method of restoring hair growth (*In re Ferens*, 417 F.2d 1072, 163 U.S.P.Q. 609 (C.C.P.A. 1969)).

such a challenge must be supported by a clear statement of "factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability." *In re Gaubert*, 524 F.2d 1222, 1225-26, 187 U.S.P.Q. 664, 666 (C.C.P.A. 1975); *see In re Brana*, 51 F.3d 1560, 1567, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995); MPEP § 706.03(a)(1).

The Final Action argues that the claimed nucleic acid molecules might not work for the disclosed utilities because the claimed nucleic acid molecules allegedly correspond to pseudogenes or are artifacts of the PCR process. The Final Action has also questioned whether the disclosure is sufficient to practice antisense technology, but has failed to provide any evidence supporting this position. Final Action at page 13. These arguments have no basis in fact. It is "always possible to theorize some combination of circumstances which would render a claimed composition...inoperative, but the art-skilled would assuredly not choose such a combination." *Ex Parte Cole*, 223 U.S.P.Q. 94, 95-96 (B.P.A.I. 1983). Furthermore, the Examiner has provided no evidence that the claimed nucleic acid molecules will not work for the disclosed utilities.

Applicants have explicitly identified specific and substantial utilities, not only in the specification, but in Applicants' Response dated July 6, 1999 ("Applicants' First Response") at pages 4-11 and in Applicants' Second Response at pages 7-15. In addition, Applicants have provided evidence in the form of a declaration under 37 C.F.R. 1.132 that the claimed nucleic acids work for at least two of the asserted utilities: use to identify the presence or absence of a polymorphism; and use as a hybridization probe for expression profiling. *See* Wiegand Decl. Either proven utility alone is enough to satisfy the law. "To violate [35 U.S.C.] 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 U.S.P.Q.2d 1401, 1412 (Fed. Cir. 1992). Unless and until the Examiner can prove that the claimed invention is wholly inoperative, which would require disproving Applicants' evidence of operability, the rejection must be withdrawn.

(a) The Claimed Nucleic Acid Molecules Do Not Correspond to Pseudogenes

The Final Action asserts that "it is not true that an EST definitely corresponds to a functional gene or gene product...because the EST may correspond to a pseudogene" and "as such the asserted basis for utility that an EST relates to an mRNA functional in vivo is illusory." Final Action at page 6.[22] As purported support for this assertion, the Final Action cites to Brandt *et al.*, *Curr. Genet.* 24.4: 330-36 (1993); Quinones *et al.*, *Plant Mol. Biol.* 31.4:937-43 (1996); Mundel *et al.*, *Curr. Genet.* 30.5: 455-60 (1996); and Barakate *et al.*, *Mol. Biol.* 229.3:797-801 (1993). The Final Action's reliance on the first three references is misplaced because it fails to appreciate the physical differences between mitochondrial mRNAs and nuclear mRNAs.

Mitochondrial mRNAs lack the polyA tails which nuclear mRNAs possess. Indeed, cDNAs, from which an individual EST may be isolated,[23] are often generated using primers that bind to the polyA tails of nuclear mRNAs. Clonetech's SMART cDNA kits, which were used to isolate ESTs in the present application, use such primers (Clonetech, Palo Alto, California). *See* Specification at page 67, lines 15-19. Accordingly, cDNAs, such as the one disclosed in the present application, which are generated using an oligo d(T) primed reverse transcriptase reaction, will not normally contain copies of mitochondrial mRNA. Wiegand Decl. at para. 5.[24]

As such, the Final Action cannot support this rejection by relying on the first three references cited, all of which report mitochondrial transcribed pseudogenes, because the claimed

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[22] The Advisory Action, on the one hand, concedes that the "evidence presented in the Wiegand Declaration supports Applicant's hypothesis that the disclosed EST corresponds to a single mRNA and gene that is functional in vivo" but, on the other hand, continues to argue that the disclosed EST "may be derived from a transcribed pseudogene." Advisory Action at page 5.

[23] ESTs are partial sequences of cDNA clones. A cDNA, by definition, has a complementary base sequence to an mRNA molecule.

[24] While the possible existence of cDNA clones that correspond to mitochondrial mRNA in a collection cannot be completely discarded, such cDNA clones are rare. Such rare possibilities cannot support speculation that the claimed nucleic acid molecules correspond to mitochondrial mRNA and not nuclear mRNA that performs a function *in vivo*. That is particularly the case for SEQ ID No. 1, which is not similar to any known mitochondrial sequence. Wiegand Decl. at para. 5.

nucleic acids were generated from a cDNA collection which, as explained above, is unlikely to contain copies of mitochondrial mRNA. Furthermore, the Wiegand Declaration provides evidence that "SEQ ID NO: 1 is not similar to any known mitochondrial sequence." Wiegand Decl. at para. 5. Therefore, because SEQ ID No. 1 is not similar to known mitochondrial sequences, it is more likely than not that it is not derived from mitochondrial DNA or a mitochondrial transcribed pseudogene.[25] Therefore, the references do not support the supposition that the claimed nucleic acid molecules correspond to pseudogenes.

Furthermore, the fourth cited reference, Barakate *et al.*, does not, as the Final Action contends, even disclose the "phenomenon of transcribed pseudogenes." Final Action at page 6. At page 801, Barakate *et al.* report, "[w]e asked whether the exoPG pseudogenes were transcribed. No transcript corresponding to the size of the exoPG pseudogenes was detected."

Accordingly, the references cited in the Final Action fail to support in any way whatsoever the assertion of an illusory correspondence between a cDNA and an mRNA. In sum, the contention that the claimed nucleic acid molecules correspond to a pseudogene is pure speculation not backed up by any of the cited documents. Furthermore, the Advisory Action recognizes that the Wiegand Declaration presents evidence disproving the speculative illusory correspondence, Advisory Action at page 5, and evidence proving that the claimed nucleic acid molecules work for at least one utility disclosed in the specification, Advisory Action at 13, but now begins to speculate why this evidence is purportedly insufficient. The Examiner's burden is to provide evidence in support of a rejection, not speculation. No such evidence has been provided here, either to establish the original argument made in the Final Action, or to refute the evidence Applicants have provided in the Wiegand Declaration.

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[25] The Advisory Action asserts that the Wiegand Declaration "does not provide any evidence that the EST of the claimed nucleic acid molecules is not derived from the mRNA of a transcribed pseudogene." Advisory Action at page 5. It is not Applicants' burden to disprove every unsubstantiated hypothesis that can be imagined. The Wiegand Declaration, in combination with the teachings of the cited references, shows that it is more likely than not that SEQ ID No. 1 is not derived from a transcribed pseudogene. This evidence cannot be ignored.

(b) The Claimed Nucleic Acid Molecules Are Not Artifacts

The Final Action also asserts that "it is more likely than not that the EST disclosed as SEQ ID NO:1 is an artifact that does not correspond sufficiently to a naturally occurring soybean nucleic acid." Final Action at page 6. This is not the case. To support the assertion that the claimed nucleic acid molecules are artifacts, the Final Action points to a number of purported technical problems. Quite apart from whether these purported problems are even real, they do not individually or together lend support to the erroneous conclusion that the EST is an artifact that would not work for the disclosed utilities.

First, the Final Action suggests that the process of polymerase chain reaction ("PCR") is error prone, and that a significant fraction of the final nucleic acid molecules contain misincorporated nucleotides. Final Action at page 4.[26] But the Final Action failed to show or even argue that because PCR misincorporates nucleotides, molecules containing misincorporated nucleotides will not work for disclosed utilities. Indeed, the contrary is true. Notwithstanding misincorporation of nucleotides, PCR-generated nucleic acid molecules are routinely and effectively used in the industry. Wiegand Decl. at para. 8.

Second, the Final Action states "it is more likely than not that the disclosed EST, SEQ ID NO: 1, is derived from a repeated sequence, and there is a significant chance that it is a chimera of related sequences." Final Action at page 5 (emphasis added). Again the Final Action has failed to show or argue that even if this statement is true, the resulting nucleic acid molecules will not work for the disclosed utilities. Equally important is the fact that chimeric and repeated cDNAs are significantly rarer than the Final Action suggests (*see* Wiegand Decl. at para. 8),[27]

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[26] Oddly, the Advisory Action (at page 4) cites the Wiegand Declaration at para. 8 as support for this statement, although the Wiegand Declaration actually states that "[t]he generation of chimeric and/or repeated DNA may occur during PCR, but such events are not common and are readily detected and avoided."

[27] The Advisory Action asserts that the Wiegand Declaration "does not provide any evidence to support the statement" that the generation of chimeric and/or repeated DNA is uncommon. Advisory Action at page 4. This is wrong. The statements contained in the Wiegand Declaration are themselves evidence. The case of *In re Alton* is particularly helpful in correcting the apparent misunderstanding here as to the nature of declaratory evidence. In *Alton*, the Examiner initially gave "little weight" to statements made in a declaration because he believed it "[did] not

and the unsupported speculation that they might exist within the disclosed EST does not provide a reasonable basis upon which a utility rejection can be made.

It is not Applicants' burden to prove a negative,[28] rather it is the Examiner's burden (not met here) to establish a reasonable basis for challenging the operability of the claimed nucleic acid molecules. *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). The Examiner has not met that burden. On the other hand, Applicants have clearly demonstrated that a nucleic acid molecule having SEQ ID No. 1 was synthesized and that it hybridized to a naturally occurring nucleic acid molecule in soybean. Wiegand Decl. at paras. 16-19. This hybridization ability is all that is necessary to practice many of the disclosed utilities, and is the feature which enables nucleic acid molecules with EST sequences to be routinely used, for example, to detect expression levels of corresponding naturally occurring soybean nucleic acids. Wiegand Decl. at para. 14. The fact that such molecules work (and work routinely) for that intended purpose is alone sufficient to establish that the claimed nucleic acid molecules possess requisite legal utility.

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point to inherent support or evidence to support the conclusory statement in paragraph 9J." 76 F.3d 1168, 1173-74, 37 U.S.P.Q.2d 1578, 1583 (Fed. Cir. 1996). The Federal Circuit held that the Examiner was in error and that the statements made in the declaration were themselves factual evidence. 76 F.3d at 1175, 37 U.S.P.Q.2d at 1583. Just as the statements in the *Alton* declaration were themselves factual evidence, the statements in the Wiegand Declaration are likewise factual evidence.

[28] The Advisory Action claims that the "specification fail[ed] to provide sufficient detail on the PCR method employed...to ensure that the EST was not chimeric or did not contain repeated sequences....at the time the application was filed." Advisory Action at page 4. This assertion is factually and legally unsound. First, the specification provides extensive guidance on PCR and PCR-based methods at, *e.g.*, page 25 line 12 to page 27, line 2, and page 29, line 26 to page 35, line 3 (and cited references). It is hard to imagine what further guidance could be provided. Second, as the generation of chimeric and/or repeated sequences during PCR is uncommon (Wiegand Decl. at para. 8), a skilled artisan would not be led to believe that the claimed nucleic acid molecules contain such sequences from the specification as filed. *Cf. Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 U.S.P.Q. 881, 883-84 (C.C.P.A. 1980) (applicant need not prove that an established utility is a statistical certainty). Even so, the evidence provided by the Wiegand Declaration at paras. 16-18 disproves this possibility. The apparent assertion that the Wiegand Declaration is inadmissible because it contains evidence that "was not disclosed in the specification" is wrong as a matter of law, as is more fully addressed in Section 8.B, *supra*.

D. The Claimed Nucleic Acids Are Enabled by the Specification

The enablement of the claimed nucleic acid molecules has been challenged in two different ways by the Final Action. First, claims 1-3 were rejected as non-enabled because the claimed nucleic acid molecules allegedly lack utility and therefore cannot be enabled. Final Action at page 2. Second, claims 1 and 3 were rejected as non-enabled because one skilled in the art would allegedly not be able to implement the use of the claimed nucleic acids as hybridization probes or amplification primers. Final Action at pages 17-18. Both rejections must be reversed in light of Applicants' factual showing of use of the claimed nucleic acid molecules to identify the presence or absence of a polymorphism and as hybridization probes, because it is well-established law that "the enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins University v. CellPro*, 152 F.3d 1342, 1361, 47 U.S.P.Q.2d 1705, 1719 (Fed. Cir. 1998) (emphasis added), *quoting Engel Indus. v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 U.S.P.Q.2d 1300, 1304 (Fed. Cir. 1991).

(1) The Claimed Invention Is Enabled Because It Has Utility

The first enablement rejection erroneously rejected claims 1-3 under 35 U.S.C. § 112, first paragraph, as not enabled by the specification, because the claimed invention allegedly lacks utility and therefore cannot be enabled. Final Action at page 2. This rejection has been overcome by the arguments stated above regarding utility, and by Applicants' submission of evidence in the form of a declaration under 37 C.F.R. 1.132 – from a scientist skilled in the art – which shows that a person skilled in the art can use and has used the claimed nucleic acid molecules for the disclosed utilities. *See* Wiegand Decl. Unless and until the Examiner comes forth with evidence to rebut the objective truth of the utilities disclosed in the specification and proven to work by the Wiegand Declaration, this enablement rejection must be withdrawn as improper. *See In re Wright*, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir.

1993); *Ex parte Lemak*, 210 U.S.P.Q. 306, 307 (Bd. App. 1981) ("pure conjecture" does not substantiate rejection for lack of enablement).

(2) The Claimed Invention Is Enabled Because One Skilled in the Art Would Know How to Use the Nucleic Acids of Claims 1 and 3

The Final Action rejected claims 1 and 3 under 35 U.S.C. § 112, first paragraph, as not enabled by the specification because it asserts that one skilled in the art would not be able to implement the use of the nucleic acids of claims 1 and 3 as hybridization probes or amplification primers. Final Action at pages 17-18. This rejection is improper on its very face, because it is made only in reference to two disclosed uses of the claimed nucleic acid molecules.[29] The enablement requirement is met if the specification enables at least one mode of using the claimed invention. *Johns Hopkins University v. CellPro*, 152 F.3d 1342, 1361, 47 U.S.P.Q.2d 1705, 1719 (Fed. Cir. 1998).

Furthermore, the Final Action admits that those skilled in the art would know how to use nucleic acid molecules "consisting" of SEQ ID No. 1, but provides no reasons why those of skill in the art would not also know how to use nucleic acid molecules "comprising" and "consisting essentially of" SEQ ID No. 1. Final Action at pages 17-18. The Advisory Action admits that those skilled in the art would know how to use the nucleic acid molecules of claims 1 and 3 that "either consist of SEQ ID NO: 1 or comprised additional sequences that would not interfere with hybridization or PCR amplification of a target sequence comprising SEQ ID NO: 1." Advisory Action at page 19.

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[29] The Advisory Action asserts that "the specification does not disclose any utilities for the claimed nucleic acid molecules that does not involve using them as a probe or primer." Advisory Action at page 18. That assertion is false. The specification discloses numerous utilities for the claimed nucleic acid molecules in the non-probe/non-primer context, *e.g.*, use to identify the presence or absence of a polymorphism (*e.g.*, specification at page 28, line 3 to page 35, line 3), use as antisense molecules (*e.g.*, specification at page 64, line 19 to page 65, line 22), use to transform cells (*e.g.*, specification at page 45, line 22 to page 65, line 25), and use to raise antibodies (*e.g.*, specification at page 20, line 19 to page 24, line 2; page 65, line 26 to page 66, line 24).

The Advisory Action appears to be arguing that claims 1 and 3 are not enabled because Applicants have not detailed how to use the nucleic acid molecules of claims 1 and 3 with additional sequences that interfere with hybridization or PCR amplification, *i.e.*, sequences that would be inoperative for the disclosed utilities of use as a hybridization probe or primer. Advisory Action at page 20. This argument is contrary to well-established law.[30] Moreover, the Patent Office has admitted that the claims as written are enabled – they cannot now rewrite the claims to encompass hypothetical limitations and then argue that these hypothetical limitations are not taught. The claims must be examined as they are presented to the Patent Office.

(a) Enablement Does Not Require the Art Worker to Predict *a Priori* the Operative Species in a Claimed Genus

The Final Action contends that the test for enablement hinges on whether one skilled in the art can "predict *a priori* with a reasonable degree of certainty the identity of claimed nucleic acid molecules suitable as a probe or primer." Final Action at page 19. *See also* Advisory Action at pages 18-20.[31] To the extent that the Final Action suggests there is a requirement for precise *a priori* predictability without recourse to any experimentation, that position is without legal support. *Cf. Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984) ("[t]hat some experimentation is necessary does not preclude enablement"). The proper test of enablement in such a situation is whether the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *See In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991).

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[30] Claims are not required to exclude possibly inoperative substances. *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984) (citing *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 U.S.P.Q 46, 48 (C.C.P.A. 1974)); *Ex Parte Cole*, 223 U.S.P.Q. 94, 95 (B.P.A.I. 1983).

[31] The Advisory Action rephrases the contention, asserting that one skilled in the art cannot predict "whether any arbitrarily chosen nucleic acid sequence was or was not soybean nucleic acid or would or would not cross-hybridize with soybean nucleic acid....without knowing the identity of all soybean nucleic acid sequences." Advisory Action at page 19.

To illustrate the incorrectness of the legal argument in the Final Action, consider the claimed genus as a group of substituted 2,3-diaryl-2*H*-1-benzopyrans, some of which possess the disclosed utility of having antiestrogenic activity, *e.g.*, the compound will bind to an antiestrogen receptor but not bind to an estrogen receptor, and some of which do not. The Final Action's "test" would require an art worker to "predict *a priori* with a reasonable degree of certainty the identity of [particular benzopyrans] suitable as [antiestrogens]." *See* Final Action at page 19. This "test" would require the art worker to be able, without even entering a laboratory, to name particular benzopyrans that have antiestrogenic activity. However, that is not the *Vaeck* test. Under the *Vaeck* test, the specification is enabling if it "adequately guide[s] the art worker to determine, without undue experimentation, which [particular benzopyrans] among all those encompassed by the [group of substituted 2,3-diaryl-2*H*-1-benzopyrans] possess [antiestrogenic activity]." *In re Vaeck*, 947 F.2d at 496, 20 U.S.P.Q.2d at 1445. The *Vaeck* test recognizes proper enablement where the skilled art worker is able to determine, once a particular benzopyran has been selected from the group and based on a reasonable experiment, whether that particular benzopyran has antiestrogenic activity.

The high level of skill in the art, the extensive knowledge available to one of skill in the art, and the teachings of the present specification adequately guide the art worker to determine, after selection and without undue experimentation, which nucleic acid molecules encompassed by the claims possess the disclosed utilities. Performing routine and well-known steps cannot create undue experimentation even if it is laborious. *See In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404; *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 218-19 (C.C.P.A. 1976).

The Final Action expresses concern that "since one cannot predict the operative embodiments, the Office cannot estimate the fraction of inoperative embodiments." Final Action at page 20. The Advisory Action expresses concern that inoperative embodiments are not

enabled.[32] Advisory Action at page 19. These concerns are irrelevant. "It is not a function of the claims to specifically exclude...possible inoperative substances." *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984) (citing *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 U.S.P.Q 46, 48 (C.C.P.A. 1974)). The case law does not require "each and every compound within a claim to be equally useful for each and every contemplated application." *Ex Parte Cole*, 223 U.S.P.Q. 94, 95 (B.P.A.I. 1983).

To return to the benzopyran analogy, there is no legal requirement that each and every substituted 2,3-diaryl-2*H*-1-benzopyran be useful for each and every contemplated utility. What is required is that the art worker know how to determine, after reasonable experimentation, whether a particular benzopyran selected from the group is useful for a particular utility. The Final Action has not contended, nor can it contend that this is unachievable with the nucleic acid molecules of the present claims. Instead, an improper test has been manufactured and applied which requires (without legal authority) demonstration of *a priori* knowledge of whether a particular molecule within the claimed genus would work.

(b) An Art Worker Can Use the Claimed Nucleic Acids Without Undue Experimentation

The Final Action's assertion of non-enablement is wrongly predicated on the allegation that before the claimed nucleic acid molecules may be used as a hybridization probe or amplification primer, a skilled artisan would have to "make-and-test" a myriad of nucleic acid molecules comprising the core sequence of SEQ ID No. 1. Final Action at pages 19-20. This allegation is without basis because a skilled artisan would be guided by his knowledge of the art in view of the particular purpose for which the claimed nucleic acids would be used.

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[32] The Advisory Action asserts that "the specification fails to teach how to use" sequences comprising the recited sequence and "addition[al] soybean sequences [that] would prevent efficient use of such a combined sequence as a hybridization probe." Advisory Action at page 19.

Furthermore, even if "make-and-test" experimentation were required to optimize a particular hybridization process, such routine experimentation would not obviate enablement.

A specification must be enabling to one of skill in the art, *i.e.*, it must guide a person of skill in the art as to how to use the claimed invention without undue experimentation. *Minerals Separation v. Hyde*, 242 U.S. 261, 270-71 (1916); *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The specification is not addressed to a layperson, but rather to one skilled in the art, and the "level of skill in the art to which a specification is addressed may be quite high." *Gould v. Mossinghoff*, 229 U.S.P.Q. 1, 14 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 U.S.P.Q. 1302 (Fed. Cir. 1987). *Accord Mowry v. Whitney*, 81 U.S. (14 Wall.) 620, 644 (1871); *Loom Co. v. Higgins*, 105 U.S. 580, 585-85 (1881); *DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985); *cf. Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534, 3 U.S.P.Q.2d 1737, 1743 (Fed. Cir. 1987) (a specification "need not teach, and preferably omits, what is well known in the art"), *quoting Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

In re Wands sets forth eight factors which may be considered in determining whether a claimed invention would require undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The *Wands* factors are illustrative, and consideration of any or all of the factors is not mandatory, *i.e.*, they provide a useful analytical framework which may be used to organize and consider the whole of the evidence on enablement. *See, e.g., Enzo Biochem v. Calgene*, 188 F.3d 1362, 1371 (Fed. Cir. 1999) (not necessary to review all of *Wands* factors); *Amgen v. Chugai Pharmaceutical*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016, 1027 (Fed. Cir. 1991) (the *Wands* factors are "illustrative, not mandatory"); *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (determination of undue experimentation is "a conclusion reached by weighing many factual considerations"). A reasonable analysis of these

factors leads to the conclusion that it would not require undue experimentation to use the nucleic acid molecules of claims 1 and 3.

The first factor is the quantity of experimentation necessary. A considerable amount of experimentation is permissible if it is routine. *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. While the claimed invention encompasses a class of nucleic acid molecules, it is well within the routine skills of a person of ordinary skill in the art to use many members of that class as hybridization probes or amplification primers. Furthermore, the "make-and-test" quantum of experimentation is reduced by the extensive knowledge, for example of hybridization and primer parameters, to which a person of ordinary skill in the art has access. *See, e.g.*, the hybridization parameters set forth in Sambrook *et al.* (eds.), *Molecular Cloning: A Laboratory Manual*, 2d ed., pp. 9.47-11.61, Cold Spring Harbor Laboratory Press, Plainview, New York (1989) and Haymes *et al.*, *Nucleic Acid Hybridization, A Practical Approach*, IRL Press, Washington, DC (1985). Accordingly, the addition of nucleotides to the recited sequence that would not alter the hybridization ability of such nucleic acid molecules is well within the skill of those working in this technology. *See* Wiegand Decl. at para. 13; Advisory Action at page 19.[33]

The second and third factors are the amount of direction or guidance presented, and the presence or absence of working examples. The specification provides guidance to those of ordinary skill in the art. One example of the guidance provided is the citation to, and incorporation by reference of, standard resource materials that describe specific conditions and procedures for the construction, manipulation, and isolation of macromolecules. Specification at page 66, line 26 through page 67, line 6. Other examples of the guidance provided are the disclosure of illustrative hybridization conditions (specification at page 17, lines 8-21), the

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[33] The Advisory Action "acknowledges that a range of small nucleic acid sequences are routinely added to nucleic acids to be used as probes or primers, such as primer binding sequences for nested PCR reactions and binding sites for capture probes for amplifying hybridization signals, or linkers and adapters for cloning and vector backbones for maintenance and production of a probe." Advisory Action at page 19.

citation of references setting forth methodology that includes the hybridization of nucleic acid molecules to detect polymorphisms (specification at page 29, line 6 through page 35, line 3), the use of primers to amplify nucleic acids in polymerase and ligase chain reactions, and in oligonucleotide ligation assays (specification at page 29, line 26 through page 31, line 24), the hybridization of nucleic acid molecules for *in situ* hybridization (specification at page 38, lines 10-22), and the hybridization of nucleic acid molecules for microarray analysis (specification at page 40, lines 14-22). The working examples in the specification, Examples 1 and 2, disclose hybridization steps and usage of primers. In particular, the working examples disclose a sequencing reaction that has a hybridization step where a universal primer hybridizes to a sequence present in pSport immediately 5-prime to the cDNA insert from which the disclosed sequence was obtained.

The fourth factor focuses on the nature of the invention, *i.e.*, nucleic acid molecules comprising, consisting of, or consisting essentially of SEQ ID No. 1 or its complement. The specification describes the nucleic acid sequence of SEQ ID No. 1, and the Final Action has admitted that this description enables nucleic acid molecules "consisting of" SEQ ID No. 1 and its complement. Final Action at pages 17-18. Moreover, the Advisory Action admits that nucleic acid molecules "comprising" and "consisting essentially of" SEQ ID No. 1 (the same sequence as in claim 2) which are operative as hybridization probes or primers are enabled. Advisory Action at pages 19-20. The nature of the invention involves using the claimed nucleic acid molecules in a variety of processes that involve a hybridization step. Practitioners in this art have available to them considerable knowledge on the conditions and approaches that can be utilized for such a step. Practitioners in this art are also prepared to try multiple methods to obtain the desired result. Wiegand Decl. at paras. 10-11.

The fifth and sixth factors focus on the state of the art and the relative skill in the art. Methods needed to practice the invention are known in the art, as well as procedures to carry out

the hybridization or primer steps. *See, e.g.*, Sambrook *et al.* (eds.), *Molecular Cloning: A Laboratory Manual*, 2d ed., Cold Spring Harbor Laboratory Press, Plainview, New York (1989); Mailga *et al.*, *Methods in Plant Molecular Biology*, Cold Spring Harbor Laboratory Press, Plainview, New York (1995); Birren *et al.*, *Genome Analysis: Analyzing DNA*, 1, Cold Spring Harbor Laboratory Press, Plainview, New York (1997); Haymes *et al.*, *Nucleic Acid Hybridization, A Practical Approach*, IRL Press, Washington, DC (1985). These references are available to guide use of the claimed nucleic acid molecules. It is clear from these resources, and particularly the guidance that they give on how to carry out hybridization and amplification steps, that a person of ordinary skill in the art would be able to use the claimed nucleic acid molecules for the disclosed utilities.

The seventh factor considers the predictability of the art. The art to be considered here is the art associated with hybridization and amplification, and with modifying nucleic acids for use in hybridization and amplification protocols. While the "performance characteristics" of a given nucleic acid within the scope of the claimed invention may, in certain circumstances, be difficult to predict, that is not relevant to an enablement analysis.[34] Use enablement does not require *a priori* predictability. The proper enablement analysis is whether the art is sufficiently predictable such that the art worker can reliably determine "which species among all those encompassed by the claimed genus possess the disclosed utility." *See In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). The arts of hybridization and amplification are sufficiently predictable such that a person of ordinary skill in the art can advantageously rely upon this predictability when undertaking the disclosed utilities with the claimed nucleic acid molecules.

The eighth factor focuses on the breadth of the claims. Use enablement is satisfied when the disclosure "adequately guide[s] the art worker to determine, without undue experimentation,

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[34] For a more detailed explanation of this point, see Section 8.C.(2).(a), *supra*.

which species among all those encompassed by the claimed genus possess the disclosed utility." *See In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). Here, enablement is satisfied because the art worker is guided by the disclosure to look, for example, to known hybridization parameters in making that determination. Use of the traditional open and semi-open transitional terms, *i.e.*, "comprising" and "consisting essentially of," in the rejected claims does not alter the fact that the claims are enabled, particularly because not every species encompassed by the claims needs to be disclosed, even in an unpredictable technology. *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Consideration of the *Wands* factors as a whole clearly establishes that undue experimentation would not be required to practice the invention. The specification provides considerable direction and guidance and provides working examples. There was a high level of skill in the pertinent art when the application was filed, and methods to practice the claimed invention were known. The routine experimentation that is typical in the art to optimize a hybridization or amplification process is not undue experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (U.S. Int'l Trade Comm'n 1983), *aff'd sub nom. Massachusetts Institute of Technology v. AB Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985) ("the fact that experimentation may be complex...does not necessarily make it undue, if the art typically engages in such experimentation").

E. The Specification Provides An Adequate Written Description of the Claimed Invention

The adequacy of the written description has been challenged by the Final Action because the nucleic acid molecules of claims 1 and 3 are allegedly "not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s)...had possession of the claimed invention." Final Action at page 21. The bases for the Final Action's challenge are that (1) there is "no evidence that applicants were in possession of the genus of

infinite nucleic acid molecules of claims 1 and 3," and (2) the specification does "not describe in terms of a precise physical description any and all nucleic acid molecules comprising SEQ ID No. 1." Final Action at pages 22-23. These are not proper bases for a written description rejection of a "comprising" claim. If they were, every "comprising" claim ever written would be invalid for failing to describe every nuance of the claimed invention.

Applicants have provided an adequate description of the claimed nucleic acid molecules that demonstrates to one skilled in the art that Applicants had possession of the claimed invention. Indeed, the Final Action agrees with Applicants that the specification provides an adequate written description of a nucleic acid molecule of claim 2, *i.e.*, nucleic acid molecules consisting of SEQ ID No. 1 or its complement, and therefore that Applicants are in possession of those nucleic acid molecules. Final Action at page 22. Furthermore, the Final Action has also acknowledged that Applicants have possession of, and have adequately described, vectors comprising SEQ ID No. 1. *Id.* The Final Action apparently failed to note that these vectors comprising SEQ ID No. 1 are in fact nucleic acid molecules of claims 1 and 3, because the vectors both "comprise" and "consist essentially of" SEQ ID No. 1. Therefore, the nucleic acid molecules of claims 1 and 3 are adequately described under 35 U.S.C. § 112, and the rejection must be withdrawn as improper.

(1) The Specification Reflects Applicants' Possession of the Claimed Invention

The purpose of the written description requirement is to ensure that the inventors had possession of the claimed subject matter, *i.e.*, to ensure that the inventors actually invented what is claimed. *Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479, 45 U.S.P.Q.2d 1498, 1503 (Fed. Cir. 1998); *Lockwood v. American Airlines*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997); *In re Alton*, 76 F.3d 1168, 1172, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996). If a person of ordinary skill in the art would, after reading the specification,

understand that the inventors had possession of the claimed invention, even if not every nuance, then the written description has been met. *In re Alton*, 76 F.3d at 1175, 37 U.S.P.Q.2d at 1584. A person of ordinary skill in the art, *e.g.*, a molecular biologist, would, after reading the present specification, understand that Applicants had possession of SEQ ID No. 1, and therefore, the claimed invention.

Applicants have provided the nucleotide sequence required by the claims, *i.e.*, SEQ ID No. 1, and have thus established possession of the claimed invention. The fact that the claims at issue are intended to cover molecules that include the recited sequences joined with additional sequences does not mean that Applicants were any less in possession of the claimed nucleic acid molecules.[35] It is well-established that use of the transitional term "comprising" leaves the claims "open for the inclusion of unspecified ingredients even in major amounts." *Ex parte Davis*, 80 U.S.P.Q. 448, 450 (B.P.A.I. 1948). *Accord PPG Indus. v. Guardian Indus.*, 156 F.3d 1351, 1354, 48 U.S.P.Q.2d 1351, 1353-54 (Fed. Cir. 1998); *Moleculon Research Corp. v. CBS*, 793 F.2d 1261, 1271, 229 U.S.P.Q. 805, 812 (Fed. Cir. 1986).

Furthermore, the present application describes more than just the nucleotide sequence required by the claims (SEQ ID No. 1), for example, it describes vectors comprising the claimed nucleic acid molecules (specification at page 47, line 14 through page 54, line 14), and not only describes, but also deposits, the clone from which SEQ ID No. 1 was sequenced, *i.e.*, the clone designated "LIB3049-003-Q1-E1-H7." Sequence Listing at page 1; Applicants' Third Response at page 1; La Rosa Decl. at para. 3. Furthermore, the addition of extra nucleotides or detectable labels to the nucleotide sequence of SEQ ID No. 1, for example, is readily envisioned by one of

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[35] If the Final Action is arguing that no possession is shown because the precise claim language is not used in the specification, then it goes beyond what is required by the law. It is well-settled that the description of a claimed invention need not be *in ipsis verbis*. *Gentry Gallery v. Berkline Corp.*, 134 F.3d 1473, 1479, 45 U.S.P.Q.2d 1498, 1503 (Fed. Cir. 1998); *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1583 (Fed. Cir. 1996); *Martin v. Johnson*, 454 F.2d 746, 751, 172 U.S.P.Q. 391, 395 (C.C.P.A. 1972).

ordinary skill in the art upon reading the present specification,[36] in particular at page 16, lines 1-10 (describing sequences with labels to facilitate detection), page 21, lines 1-9 (describing fusion nucleic acid molecules), page 25, lines 1-19 (describing automated nucleic acid synthesizers that can be used to build nucleic acid molecules), and page 66, line 25 through page 67, line 6 (citing references describing the construction, manipulation and isolation of nucleic acid macromolecules).

(2) Applicants Have Described the Claimed Invention

The Final Action asserts that "substantial species embraced by the claims" such as "full length mRNAs, cDNAs and genes that include SEQ ID NO:1" are not adequately described under 35 U.S.C. § 112. Final Action at page 21. The Advisory Action appears to assert that each nucleic acid molecule within the genus must be "described by complete structure." Advisory Action at page 20. These assertions are totally unfounded. An adequate written description of a genus of nucleic acids may be achieved by a "recitation of structural features common to the members of the genus." *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568-69, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). The structural feature relied upon to describe the claimed genus must be capable of distinguishing members of the claimed genus from non-members.[37] *Id.*

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[36] The Advisory Action asserts on one hand that the "specification does not disclose what characteristics these additional sequences may or may not have that are consistent with the operability of the nucleic acid molecules as probes or primers," Advisory Action at page 21, but on the other hand acknowledges that "a range of small nucleic acid sequences are routinely added to nucleic acids to be used as probes or primers." Advisory Action at page 19. Apparently the Advisory Action is arguing that Applicants must teach "conventional and well-known genetic engineering techniques" in direct contravention of established patent jurisprudence. *E.g., Ajinomoto Co. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345, 56 U.S.P.Q.2d 1332, 1337 (Fed. Cir. Oct. 3, 2000).

[37] The Advisory Action confuses the issue by asserting that "the specification provides no physical (i.e. structural) characteristics of [full length mRNAs, cDNAs and genomic sequences comprising SEQ ID NO: 1] to distinguish them from other nucleic acid molecules comprising SEQ ID NO: 1." Advisory Action at page 21. This assertion has no basis in law. The Federal Circuit has elucidated a test for written description wherein a genus of nucleic acids may be described by a structural feature that distinguishes members of the claimed genus from non-members of the claimed genus. *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568-69, 43 U.S.P.Q.2d

The claimed nucleic acid molecules are a genus of nucleic acid molecules having the common structural feature of SEQ ID No. 1 or its complement. This common structural feature is shared by every nucleic acid molecule in the claimed genus, and it distinguishes the members of the claimed genus from non-members. If a nucleic acid molecule such as an mRNA contains SEQ ID No. 1 (or its complement), then it is a member of the claimed genus. If a nucleic acid molecule does not contain SEQ ID No. 1 (or its complement), then it is not a member of the claimed genus. The presence of other nucleotides at either end of the recited sequence will not interfere with the recognition of a claimed nucleic acid molecule as such – it either contains the nucleotides of SEQ ID No. 1 (or its complement) or it does not.

A further contention of the Final Action is that the "recitation of 'consisting essentially of' in claim 3 fails to distinguish the invention of claim 3 from that of claim 1" because no "basic and novel characteristics" of the claimed invention are disclosed.[38] Final Action at page 22; Advisory Action at pages 21-22. This contention is unfounded. The specification certainly discloses the primary "basic and novel characteristic" of the claimed nucleic acid molecules, *i.e.*, the nucleotide sequence of SEQ ID No. 1. Furthermore, the transitional term "consisting essentially of" is a well-known term of the patent drafter's art,[39] and Applicants do not in any way alter the common meaning of this term. One skilled in the art would clearly know if a

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1398, 1406 (Fed. Cir. 1997). There is no requirement to distinguish certain members of the claimed genus from other members of the claimed genus.

[38] This same argument was brought up in the context of § 112, second paragraph, in the First Action at pages 10-11.

[39] *See Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 412 (Fed. Cir. 1984) (defining "consisting essentially of" as a phrase that excludes ingredients that materially affect the basic and novel characteristics of the claimed composition); *Ex parte Davis*, 80 U.S.P.Q. 448, 450 (B.P.A.I. 1948) (defining "consisting essentially of" as leaving the claim open for the inclusion of "unspecified ingredients which do not materially affect the basic and novel characteristics"). The use of the term "composition" in *Atlas Powder* is a reference to the language of Section 101, and is considered to "embrace[] chemical compounds, mechanical or physical mixtures, alloys, and a great variety of things." *Exxon Chemical Patents, Inc. v. Lubrizol Corp.*, 65 F.3d 1553 (Fed. Cir. 1995) (citation omitted). *See also In re Barr*, 444 F.2d 588 (C.C.P.A. 1971) ("chemical compounds are clearly included as one kind of composition of matter.").

nucleic acid molecule contains the nucleotide sequence of SEQ ID No. 1. One skilled in the art also knows what materially affects the basic and novel characteristics of a nucleic acid sequence,[40] especially in view of the detailed disclosure in the specification of the intended uses for the claimed nucleic acid sequences. Thus, both claims 1 and 3 satisfy the written description requirement.[41]

CONCLUSION

In view of the foregoing, it is respectfully requested that the Board of Patent Appeals and Interferences reverse the Rejections and that the subject application be allowed forthwith.

Respectfully submitted,

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[40] The Advisory Action acknowledges that many "nucleic acid sequences are routinely added to nucleic acids to be used as probes or primers," Advisory Action at page 19, which in essence is an acknowledgement that one skilled in the art knows what materially affects the ability of a nucleic acid to be used as a probe or primer.

[41] To the extent that the Final Action's argument is in fact a mislabeled indefiniteness argument based on § 112, second paragraph, claims 1 and 3 have also been shown to satisfy the definiteness requirement.

APPENDIX A

1. A nucleic acid molecule isolated from other nucleic acid molecules and comprising SEQ ID No. 1 or its complement.

2. A nucleic acid molecule consisting of SEQ ID No. 1 or its complement.

3. A nucleic acid molecule isolated from other nucleic acid molecules and consisting essentially of SEQ ID No. 1 or its complement.